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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte HARRY R. DAVIS,
TEDDY KOSOGLOU, and GILLES J. PICARD

Appeal 2010-003020[1]
Application 10/057,323
Technology Center 1600

Decided: March 9, 2010

Before TONI R. SCHEINER, DONALD E. ADAMS, and
LORA M. GREEN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 32, 102-104, 106-108, 110-112, and 126. We have jurisdiction under 35 U.S.C. § 6(b).

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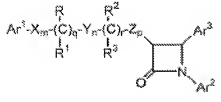
[1] This Appeal is related to Appeal No. 2007-0181, decided June 28, 2007.

STATEMENT OF THE CASE

Claim 32 is representative of the claims on appeal, and reads as follows:

32. A composition comprising:
(a) at least one peroxisome proliferator-activated receptor activator;
(b) at least one sterol absorption inhibitor represented by Formula (I):



(I)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, or prodrugs of the compounds of Formula (I) or of the isomers, salts or solvates thereof, wherein in Formula (I) above:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-;

R and R^2 are independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ and $-O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-}$

$_{10}$-$COOR^6$, -$O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, -CH=CH-$COOR^6$, -CF_3, -CN, -NO_2 and halogen;

R^5 is 1-5 substituents independently selected from the group consisting of -OR^6, -$O(CO)R^6$, -$O(CO)OR^9$, -$O(CH_2)_{1-5}OR^6$, -$O(CO)NR^6R^7$, -NR^6R^7, -$NR^6(CO)R^7$, -$NR^6(CO)OR^9$, -$NR^6(CO)NR^7R^8$, $NR^6SO_2R^9$, -$COOR^6$, -$CONR^6R^7$, -COR^6, -$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, -$O(CH_2)_{1-10}$-$COOR^6$, -$O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and -CH=CH-$COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; and

(c) at least one cardiovascular agent selected from the group consisting of calcium channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin converting enzyme (ACE) inhibitors, antihypertensive, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof.

Appellants were required by the Examiner to elect a species of peroxisome proliferators-activated receptor (PPAR) activator, sterol absorption inhibitor, and a third therapeutic agent. (App. Br. 2.) Appellants elected fenofibtate as the PPAR activator, ezetimibe as the sterol absorption inhibitor, and captopril as the third therapeutic agent. (*Id.* at 2-3.)

The Examiner relies on the following evidence:

Rosenblum et al.	US 5,846,966	Dec. 8, 1998
Bergey et al.	EP 0 457 514 A1	Nov. 21, 1991

Sucralose – A New Artificial Sweetener, 40 THE MEDICAL LETTER ON DRUGS AND THERAPEUTICS 67-70 (1998).

Appellants rely on the following evidence:

Michael Farnier, *Ezetimibe plus fenofibrate: a new combination therapy for the management of mixed hyperlipidaemia?* 8 EXPERT OPIN. PHARMACOTHER 1345-1352 (2007).

We affirm.

ISSUE

Did the Examiner provide a sufficient reason to combine Rosenblum, Medical Letter, and Bergey to arrive at the claimed composition comprising ezetimibe, fenofibrate, and captopril?

FINDINGS OF FACT

FF1 This is the second time this case has been before us on appeal.

FF2 In Appeal No. 2007-0181, we determined that the combination of Rosenblum, Medical Letter, and a third reference, Katzung, rendered obvious a combination of ezetimibe, fenofibrate, and niacin. (Decision, pp. 6-7.)

FF3 That conclusion was based on the rationale that all three compounds are known in the art to be useful for lowering serum cholesterol. (*Id.* at 7.)

FF4 The Examiner rejects claims 32, 102-104, 106-108, 110-112, and 126 under 35 U.S.C. § 103(a) over the combination of Rosenblum, Medical Letter, and Bergey. (Ans. 4.) As Appellants do not argue the claims separately, we focus our analysis on independent claim 32. Merely pointing out differences in what the claims cover is not an argument as to why the claims are separately patentable. 37 CFR § 41.37(c)(1)(vii).

FF5 The Examiner relies on Rosenblum for teaching that ezetimibe is useful for reducing cholesterol levels and the risk of atherosclerosis. (Ans. 4.)

FF6 Specifically, Rosenblum teaches that the disclosed compounds, such as ezetimibe, lower serum lipid levels, and in particular, serum cholesterol levels. (Rosenblum, col. 20, ll. 39-40.)

FF7 Rosenblum teaches further that the compounds "inhibit the intestinal absorption of cholesterol and . . . significantly reduce the formation of liver cholesteryl esters," and are thus hypocholesterolemic agents, useful in the treatment and prevention of atherosclerosis. (*Id.* at col. 20, ll. 42-48.)

FF8 Rosenblum also teaches that the compounds of the invention, such as ezetimibe, may be administered in combination with a cholesterol biosynthesis inhibitor. (*Id.* at col. 21, ll. 26-28.)

FF9 Rosenblum teaches that the compounds "are hypocholesterolemic agents by virtue of their ability to inhibit the intestinal absorption and/or esterification of cholesterol." (*Id.* at col. 20, ll. 44-46.)

FF10 The Examiner relies on Medical Letter for teaching that fenofibrate is useful in reducing serum cholesterol levels. (Ans. 4.)

FF11 Specifically, Medical Letter teaches that fenofibrate is used in the treatment of hypertriglyceridemia. (Medical Letter 68.) According to Medical Letter, fenofibrate increases lipoprotein lipase activity and triglyceride clearance, and that fenofibrate decreases LDL cholesterol. (*Id.*)

FF12 The Examiner relies on Bergey for teaching that captopril "significantly reduce[s] serum cholesterol in hypercholesterolemic patients,"

and is beneficial as an anti-atherosclerotic agent to slow or regress the progress of atherosclerosis. (Ans. 4.)

FF13 The Examiner further cites Bergey for teaching "the combination of captopril with an additional cholesterol lowering agent such as HMG-CoA reductase inhibitors." (*Id.*)

FF14 Bergey specifically teaches a method of preventing, stabilizing, or causing regression of atherosclerosis by combining an HMG CoA reductase with an ACE inhibitor. (Bergey 8, ll. 18-22.)

FF15 Bergey teaches that the "removal of multiple atherogenic stimuli by administration of an appropriate drug combination . . . is of greater therapeutic benefit than monotherapy." (*Id.* at 8, ll. 34-35.)

FF16 Bergey teaches that "[c]holesterol lowering drugs or drugs which are inhibitors of cholesterol biosynthesis which may be used in the method of the invention include HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, bile acid sequestrants, probucol, niacin and the like." (*Id.* at 8, ll. 44-46.)

FF17 The Examiner notes that "[t]he references do not expressly teach a composition comprising fenofibrate . . .[,] ezetimibe, and captopril together." (Ans. 4.)

FF18 The Examiner concludes that it would have been obvious to the ordinary artisan at the time of invention to combine ezetimibe, fenofibrate, and captopril together into a single composition as the prior art teaches that all three compounds are "useful in reducing cholesterol and reduce the risk of atherosclerosis individually." (*Id.* at 5.) The Examiner cites *In re Kerkhoven*, 626 F.2d 846 (CCPA 1980) in concluding that "combining two

or more agents, which are known to be useful to reduce cholesterol and reduce the risk of atherosclerosis individually, into a single composition useful for the very same purpose is *prima facie* obvious." (Ans. 5.)
FF19 Farnier, cited by Appellants, teaches that the exact mechanism of action of ezetimibe has not been fully elucidated, but that the compound effectively inhibits the intestinal absorption of cholesterol and plant sterols. (Farnier 1346.)

PRINCIPLES OF LAW

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

The Supreme Court has recently emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). *See also id.* at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416.

In addition, it is prima facie obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in

order to form a third composition which is to be used for the same purpose. *In re Susi*, 440 F.2d 442, 445 (CCPA 1971); *In re Crockett*, 279 F.2d 274, 276-77 (CCPA 1960). The idea of combining the compositions flows logically from their having been individually taught in the prior art. *Kerkhoven*, 626 F.2d at 851.

ANALYSIS

Appellants argue that: "the combination of references cited as rendering the claimed invention obvious is improper because there is no rationale for making a triple combination treatment of the claimed components of a sterol absorption inhibitor . . . (e.g., ezetimibe)[ ], a PPAR activator (such as fenofibrate) and a cardiovascular agent (such as the ACE inhibitor captopril) as defined in claim 32." (App. Br. 7-8.)

Appellants assert that *Kerkhoven* rationale relied upon by the Examiner is based on improper hindsight reconstruction of the claims. (App. Br. 8.) Appellants argue that "the Examiner has culled individual compounds from three prior art references to form the claimed triple composition," but that the rationale used by the Examiner "overlooks certain aspects of the prior art that would suggest to one skilled in the art that no such combination is warranted." (*Id.*)

Specifically, Appellants argue Medical Letter teaches at page 68 that fenofibrate is not as effective as the statins in lowering LDL cholesterol, a major risk factor in atherogenesis, thus "there is no reason to combine a PPAR activator such as fenofibrate with the ezetimibe compound disclosed in Rosenblum." (*Id.* at 8-9.) Appellants argue further that the references

relied upon by the Examiner do not provide a reason to combine an ACE inhibitor such as captopril with ezetimibe. (*Id.* at 9.) Bergey, Appellants assert, states that there is no evidence that ACE inhibitors result from inhibition of the cholesterol synthetic pathway, and thus their mechanism of action is different from that of the HMG CoA reductase inhibitors such as statins. (*Id.*) According to Appellants, Bergey then proposes "a combination of a HMG CoA reductase inhibitor and an ACE inhibitor" as "combination therapy of drugs known to have separate mechanisms of action is preferred over monotherapy since co-administration can produce a maximum therapeutic effect which is greater than can be achieved when either drug is given alone." (*Id.*) Appellants argue, citing Farnier, that the mechanism of action of ezetimibe was unknown at the time of filing, and thus the ordinary artisan would not have combined ezetimibe, fenofibrate, and captopril without an understanding of the mechanism of action of ezetimibe. (*Id.*)

Appellants' arguments have been carefully considered, but are not convincing. We agree with the Examiner that it would have been obvious to the ordinary artisan to combine ezetimibe, fenofibrate, and captopril together into a single composition as the prior art teaches that all three compounds are useful in reducing cholesterol and reduce the risk of atherosclerosis individually. Therefore, the art recognized property of each of the described agents as a cholesterol lowering agent would have provided one of ordinary skill in the art with ample suggestion of their combination in the composition as claimed.

With respect to Appellants' argument that neither Rosenblum nor Medical Letter provides motivation for substituting a PPAR such as fenofibrate for the statin used in combination with the ezetimibe as taught by Rosenblum, as Medical Letter teaches at page 68 that fenofibrate is not as effective as the statins in lowering LDL cholesterol, a major risk factor in atherogenesis, we disagree. "A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005) (citations omitted).

Moreover, we find Appellants' argument that one would not have combined ezetimibe, fenofibrate, and captopril without an understanding of the mechanism of action of ezetimibe to be factually inaccurate, as the action of ezetimibe is known: That is, as set forth in claim 32, Rosenblum, and Farnier, ezetimibe is known to inhibit the intestinal absorption of cholesterol. Thus, it would have a different mode of lowering cholesterol than fenofibrate, which is a PPAR activator, and captopril, an ACE inhibitor. Bergey teaches the use of combination therapy, and suggests agents with many different modes of action, such as ACE inhibitors with "[c]holesterol lowering drugs or drugs which are inhibitors of cholesterol biosynthesis which may be used in the method of the invention include HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, bile acid sequestrants, probucol, niacin and the like." (FF16.) Thus, the ordinary artisan would not be dissuaded from combining captopril with ezetimibe and fenofibrate, as all three compounds are known to be useful to reduce cholesterol and reduce the risk of atherosclerosis individually.

CONCLUSION OF LAW

We conclude that Examiner provided a sufficient reason to combine Rosenblum, Medical Letter, and Bergey to arrive at the claimed composition comprising ezetimibe, fenofibrate, and captopril.

We thus affirm the rejection of claims 32, 102-104, 106-108, 110-112, and 126 under 35 U.S.C. § 103(a) over the combination of Rosenblum, Medical Letter, and Bergey.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc

MERCK
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